To treat or not to treat: puberty suppression in childhood onset gender dysphoria

Rosalia Costa [1], Polly Carmichael [1] and Marco Colizzi [2]

[1] Gender Identity Development Service, Tavistock and Portman NHS Foundation Trust, Tavistock Centre, 120 Belsize Lane, London NW3 5BA.[2] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park London SE5 8AF, UK. Correspondence to: R.C. rcosta@tavi-port.nhs.uk

Abstract | Puberty suppression using gonadotropin-releasing-hormone analogues (GnRHa) has become increasingly accepted as an intervention during the early stages of puberty (Tanner stage 2–3) in individuals with clear signs of childhood onset gender dysphoria. However, lowering the age threshold for using medical intervention for children with gender dysphoria is still a matter of contention, and is more controversial than treating the condition in adolescents and adults, as children with gender dysphoria are more likely to express an unstable pattern of gender variance. Furthermore, concerns have been expressed regarding the risks of puberty suppression, which are poorly understood, and the child's ability to make decisions and provide informed consent. However, even if the limited data available mean that it is not possible to make a conclusive treatment recommendation, some safety criteria for puberty suppression can be identified and applied.

We may suppose that there have always been people who have wished to cross the gender line in terms of attire, presentation, comfort, behaviour, and relationships. However, only in the past few decades has gender nonconformity consistently been shown to be associated with clinical distress or impairment in important areas of functioning[1], requiring clinical attention in some individuals. The work of Harry Benjamin and the World Professional Association for Transgender Health (WPATH), who in 1953 designated 'transsexualism' as an autonomous clinical entity[2], has eventually led to a recommended procedure for managing distress arising from the incongruity of assigned sex at birth and internal experience of gender. The main goals of this approach are summarized in the WPATH Standards of Care[3], which define available treatment options in order to ensure and promote the highest standards of health care for children, adolescents, and adult individuals seeking gender transitioning. This treatment programme includes hormonal and surgical interventions, which are considered after a careful diagnostic phase and only after real-life experience in the desired gender role. The WPATH Standards of Care also encourages evaluation and recommendations by mental health professionals (including assessment, counselling, and psychotherapy), and hormonal and surgical treatments. Moreover, this approach actively promotes the individual's well-being, destigmatizing gender variance, and supports the creation of a safe environment in order for children and adolescents with gender dysphoria to express themselves, and encourages parents to support their gender-variant children[4].

In 1980, the American Psychiatric Association (APA) first included the condition — known then as 'transsexualism/gender identity disorder'— in the Diagnostic and Statistical Manual (DSM)[5], acknowledging the possibility that it could exist in children or adolescents. The inclusion of gender variance in a psychiatric manual was seen by many to pathologize nonconforming gender identity and expression, and to reinforce gender stereotypes. However, substantial changes have been made to the diagnostic criteria over the subsequent 30 years, in an attempt to better define the condition and to find a balance between the competing issues of stigma and access to care[6-9]. In

2013, APA renamed the condition ‘gender dysphoria’ in order to better characterize gender-related discomfort[8].

The core feature of gender dysphoria is a marked incongruence between one’s experienced and/or expressed gender and assigned gender (usually assigned at birth, and referred to as natal gender), of at least 6 months duration. However, according to DSM-5, different diagnostic criteria apply to adults and adolescents on one hand, and children on the other. Whereas only two gender-variant behavioural manifestations are required to diagnose gender dysphoria in adults and adolescents (Box 1), six criteria are required to reach the diagnosis in children, one of which must be the clinical evidence of the child’s strong desire to be of the non-natal gender or insistence of being the non-natal gender (Box 2). Furthermore, clinically significant psychosocial distress or impairment is needed in order to diagnose gender dysphoria, regardless of the age of the individual[8].

[H1]Development of gender identity

Gender identity serves as a social identity at an individual as well as a collective level. Its development begins at an early stage of human life; research has shown that around the age of 3 years, children show a basic sense of self as male or female[10], owing to their inner experience of belonging to one gender[11, 12]. Furthermore, at 6–7 years of age a child realizes that one’s gender is likely to remain constant[13-15]. Some research suggests that a developmental lag exists in gender constancy acquisition in children with gender-variant behaviour[16]. Achieving gender constancy represents a cognitive-developmental milestone in gender identity development[17-19] and is due to the understanding that being male or female is a biological characteristic that cannot be changed by altering superficial attributes, such as hairstyle or clothing[11]. The ability to classify oneself and others as male or female also has strong affective components[20].

Epidemiological studies on the incidence and prevalence of gender-variant behaviour and gender dysphoria are usually based on patients presenting at gender identity clinics, and efforts to achieve realistic estimates are fraught with difficulties[21-24]. The incidence of gender dysphoria is regarded as remaining constant, whereas the prevalence of the condition has shown great variation between the first and the most recent studies, diverging among countries and even between different epochs within the same country. Prevalence estimates are strongly affected by recruitment strategies, diagnostic criteria, treatment availability, and eligibility[23, 24]. A 2015 meta-analysis of 21 studies concluded that the prevalence of gender dysphoria is 1 in 14,705 in adult males and 1 in 38,461 in adult females[25]. Moreover, an interesting study has indicated that the numbers of referrals to specialized clinics for gender dysphoria have increased between 2006 and 2013 together with a corresponding shift in the sex ratio, from one favouring natal males to one favouring natal females [26]. Although gender-variant behaviour has been shown to be frequent in children, ranging from 2–23% for natal males and 4–39% for natal females[27, 28], numbers are definitely smaller when considering gender-variant adolescents reporting discontent with their assigned gender and/or seeking hormone treatment or some form of surgery (0.6% of the natal males and 0.2% of the natal females)[29]. These findings seem to suggest that there isn't a direct relationship between the experience of gender-variant behaviour, the dislike of one's natal sex characteristics, and the desire to undergo sex reassignment procedures, providing support for a dimensional approach to gender dysphoria[29]. In contrast to studies of gender-variant behaviour, studies attempting to investigate the prevalence of gender dysphoria according to the DSM-5 diagnostic criteria[8] report even lower rates in adults, ranging from 0.005–0.014% for natal males and 0.002–0.003% for natal females[8].

Very little is known about the trajectory of the condition in gender-variant children who meet the criteria for a gender dysphoria diagnosis as an adult. The percentage of children initially diagnosed with gender dysphoria who display persistence of the condition ranges from 12–27%[30-32], indicating that the majority of children meeting gender dysphoria criteria do not have persistence of the

condition by the time they have entered puberty. This finding could be partially explained by the internalized social pressure to conform[33], although this hypothesis is still untested[34]. However, the possibility of an original misdiagnosis (false positive) should also be considered[33, 34]. Regardless of these limitations, it is thought that an increased number and intensity of gender-variant phenomena in childhood, gender dysphoria persistence in adolescence, and cognitive dimensions of gender identity nonconformity (rather than emotional dimensions) could predict an increased likelihood of gender dysphoria persistence into adulthood[35-37].

[H1]Clinical evidence in children

Gender variance is conceptualized as a spectrum of gender identity-related phenomena rather than a homogeneous phenomenon[24]. In an attempt to define possible gender dysphoria-related characteristics and predictors of outcome, two subtypes of gender dysphoria have been suggested, an early-onset (prepubertal) group and a late-onset (peripubertal or postpubertal) group. These groups have been summarized in the DSM-5[8]. Some researchers and clinicians have suggested that early-onset gender-dysphoric individuals might present with more constant forms of gender dysphoria or gender variance from childhood onwards than the late-onset group and identify with homosexual sexual orientation more frequently, and could benefit from early medical intervention[24, 38]. Children in the early-onset group can experience substantial distress at the physical changes of puberty and gender dysphoria can even become more intense at this time[24]. Instead, late-onset gender dysphoria individuals could present with a more fluctuating gender-variant behaviour, not necessarily needing gender reassignment[24].

Regardless of the course of the condition, it is not possible to safely differentiate between children who will show persistence of gender-variant behaviour in adulthood from those who will instead show desistence and conform to their natal gender[39]. The optimal approach to treating prepubertal children with gender dysphoria is, therefore, still a matter of contention and is more

controversial than treating the condition in adolescents and adults, who are more likely to express a stable pattern of gender variance[39]. Furthermore, research into treatment outcomes in children with gender dysphoria is still at an early stage, with a few studies which have investigated the effect of puberty suppression on psychosocial functioning and mental wellbeing[40-42]. To date, only one long-term follow-up study has indicated that a treatment protocol including puberty suppression leads to a psychosocial functioning in late adolescence that is comparable to non-gender dysphoric peers[41]. Moreover, randomized controlled trials to study treatment outcomes in children with gender dysphoria are still needed[43]. According to the WPATH Standards of Care, adolescents should be considered eligible for puberty suppression based on five criteria: evidence of gender dysphoria from early childhood onwards, an increase in the intensity of gender dysphoria after the first pubertal changes, no signs of psychiatric comorbidity, provision of adequate psychological and social support during the treatment, and demonstration of knowledge and understanding of the effects of puberty suppression by the patient[3].

[H1]Approaches to treatment in childhood

The report from the APA Task Force on treatment of gender dysphoria[39] has highlighted the challenging issue of capacity in children when considering treatment options; from a developmental point of view, children are regarded as not having the ability to make decisions and they lack the legal ability to provide informed consent. Treatment for gender dysphoria — especially puberty suppression — is particularly controversial and no agreement has been reached among clinicians and researchers on a specific care pathway for gender dysphoria in childhood. As a consequence, treatment options need to be discussed in a wider context, in which caregivers have the responsibility of making treatment decisions on the patient's behalf, with potentially lifelong consequences.

Experts and health-care providers agree that psychotherapy represents a fundamental part of treatment for gender dysphoria in childhood, in order to promote the individual's self-confidence and well-being. One study has indicated that psychological support after diagnosis has an effect on its own in improving the psychosocial functioning of gender dysphoric adolescents[40]. However, clinicians disagree on what they consider the main goal of offering psychological support to young people with gender dysphoria. Three different approaches can be identified, which use divergent clinical paradigms to address the issue of gender dysphoria in children. The first approach relies on the concept that minimization of gender-variant behaviour in children should be actively promoted in order to reduce the likelihood of gender dysphoria persistence in adulthood[43]. Personal, philosophical, or ethical considerations regarding the inappropriateness of allowing gender-variant behaviour in children, as well as practical issues, such as the high cost of gonadotrophin-releasing-hormone antagonists (GnRHa) for puberty suppression and other sexual reassignment procedures, lead some clinicians to consider persistence of gender dysphoria into adulthood undesirable[43-45]. Some clinicians criticize the medical treatment of young individuals with gender dysphoria, stating that a diagnosis of gender dysphoria cannot be made in preadolescents, as their gender identity is still fluctuating and developing[33, 34]. Other professionals fear that puberty suppression could crystallize gender dysphoria, inhibiting the development of a gender identity correspondent to the natal sex[46]. Most importantly, this approach is based on the evidence is that only a minority of those with untreated childhood gender dysphoria will identify as transsexual or transgender in adulthood, while the majority will become comfortable with their natal gender over time[33, 34, 44]. Furthermore, concerns have been raised regarding the risks of puberty suppression — including effects on brain development and other physical issues, such as bone density alteration — which are still not fully understood[39, 47]. To date, only one study has assessed the effect of GnRHa on cognition in gender dysphoria, reporting no evidence for a deleterious effect of puberty suppression on brain activity and related executive functioning[48]. Also, bone mineral density has been recently studied for the

first time in a cohort of gender dysphoria individuals receiving puberty suppression, suggesting that these individuals may face loss of bone mass if cross-sex hormonal treatment is postponed beyond the age of 16 years[49].

A second approach considers it crucial not to interfere with the child's development. Compared with the first approach, this ethos does not consider a therapeutic target to lessen gender-variant behaviour and instead promotes neutrality with respect to the patients' gender identity outcome. Like the first approach, the basis of this strategy is the absence of clear-cut predictors of gender dysphoria persistence in adulthood and the evidence that a substantial percentage of gender-variant behaviour in childhood will not culminate in adult gender dysphoria[30, 44]. The goal of this outcome is to allow the developmental trajectory of gender identity to unfold without pursuing or encouraging a specific outcome[50-52]. It does not exclude active support of the child's social integration and well-being, in order to minimize social risks and stressors, and self-recognition of gender variance can be encouraged, and behavioural, cognitive and emotional coping strategies can be promoted[50, 53, 54].

The third approach is based on the concept that abstaining from medical intervention could do even more harm to the child. In this framework, health-care professionals and carers should actively support the child's affirmation as a member of the desired gender. As a consequence, the option of endocrine treatment to suspend and/or suppress puberty should be considered, in order to facilitate a gradual and more efficient gender transition. The rationale for supporting transition before puberty is the belief that some children will still express a stable pattern of gender variance into adulthood. Enabling them to make important age-appropriate developmental transitions, puberty suppression (and subsequent sex reassignment procedures, such as cross-sex hormonal treatment and gender reassignment surgery) would contribute to a satisfactory objective and subjective well-being in young adulthood[41], and a more favourable surgical outcome[55]. Accordingly, undergoing the pubertal development of their biological sex could increase the

distress already associated with the condition, with serious risks for the individual's psychological well-being[56]. As studies have indicated that cross-sex hormonal treatment improves well-being in adults with gender dysphoria[57-59], research has begun to focus on the effects of puberty suppression on quality of life in prepubertal and adolescent individuals with gender dysphoria, indicating that this early intervention could improve their psychosocial functioning and well-being[40-42]. However, the available evidence is currently too limited to draw definite conclusions. A team from the Netherlands has been an influential leader in promoting a protocol — the so-called Dutch protocol — which recommends treatment of minors with gender dysphoria after an extensive psychological and psychiatric evaluation, with puberty suppression at the age of 12 years and after the first stages of puberty (Tanner stage 2–3) have been reached[55, 60] (Box 3). This team have also provided evidence that no young individual eligible for GnRHa has dropped out of treatment or shown regret during puberty suppression[61, 62]. The cornerstone of this approach is the evidence that, although puberty suppression seems to reduce the gender dysphoria-related distress[40-42], and seems to be a relatively safe and reversible procedure[46, 60], not treating gender dysphoria in childhood cannot be considered a neutral option, as delaying treatment until late adolescence or adulthood might lead to the development of psychiatric concerns, social isolation, and impaired functioning[46]. However, the Dutch team does consider the possibility of delaying eligibility for puberty suppression in patients with concomitant psychiatric or psychosocial difficulties requiring intervention.

[H1]Balancing observation and intervention

Although medical treatment and health risks[63] in gender dysphoric adults are well defined and have been the object of more extended research in clinical settings[57-59], the treatment strategy for young persons has received little attention in clinical research settings and is still debated[56]. According to the Task Force for gender dysphoria, specific health-care pathways for young individuals with gender dysphoria have not been properly investigated owing to the absence of

randomized or adequately controlled longitudinal studies[39]. As a consequence, conclusive treatment recommendations for puberty suppression cannot be made. Clinicians disagree about the appropriateness of puberty suppression because of their professional background and religious or ethical convictions, and the individual, their carers, or the health-care professionals could hold different views, making even more difficult to reach agreed solutions.

In their Task Force treatment recommendation, Byne and colleagues[39] suggest that any treatment decision in children presenting with gender-variant behaviour should be made only after extensive evaluation of the patient's gender-related issues, including identity, role, and behaviour, after addressing any potential concerns of the caregivers or difficulties in their relationship with the patient, and after providing psychoeducation, counselling, and informed consent to any treatment option and outcome from caregivers, in order to support their decision. Treatment should only be initiated after disclosing the limitations of the available data on both outcome and risks of the treatment, having provided information to the child that can be understood, and only in the context of the patient's mental health and psychosocial environment, including family, school, and larger community.

In an attempt to balance the benefits and risks of puberty suppression, and in light of all the available information and knowledge, our opinion is that the enlightened decision would be to allow puberty suppression when the adverse outcomes of a lack of or delayed intervention outweigh the adverse outcomes of early intervention in terms of long-term risks for the child. In other words, if allowing puberty to progress seems likely to harm the child in terms of psychosocial and mental well-being, puberty should be suspended.

[H1]A multidisciplinary approach

[H2] Psychological support

The treatment protocol for individuals with gender dysphoria should include a number of different components in order to promote the most satisfactory outcome[64, 65]. The two main goals of gender dysphoria treatment are to support the patient's transition, aligning the phenotype with the experienced and/or expressed gender identity, and to support their psychosocial well-being. These outcomes are interlinked and are better achieved using a multidisciplinary approach, involving both physical and nonphysical interventions[41].

Although medical and surgical interventions are fundamental to obtaining a physical appearance in line with the desired gender, psychotherapy and psychological support are considered of great importance in helping the individual to identify and work through the factors that will contribute to his or her decision to undergo cross-sex medical intervention. Psychological and psychotherapeutic settings give patients the opportunity to discuss their behaviour, emotions, and ideas with regard to themselves and possible life problems or events[40]; gender dysphoric individuals can experience discomfort with their gender incongruence as a result of internalizing society's normative gender expectations, discrimination, and prejudice[66]. Finally, psychological interventions are also important in the management of posthormonal and surgical outcomes, in order to promote the patient's sense of control and psychological integration of gender role and identity[67]. Thus, psychological support is essential in the assessment, formulation and clinical management of gender dysphoria, owing to the complexity and specific needs of gender dysphoric individuals at different ages. A variety of psychotherapeutic and psychosocial interventions for gender dysphoria in children are well established, including individual insight-oriented psychoanalytic or psychodynamic psychotherapy, protocol-driven psychotherapy such as behaviour modification, parent and peer relations-focused therapy, and parent and child therapeutic groups, along with educational approaches[39].

[H2] Physical interventions

Physical interventions for gender dysphoria fall into two main categories or stages: cross-sex hormonal therapy and gender-reassignment procedures. Hormonal treatment involves the administration of cross-sex hormones and is intended to induce the sexual characteristics of the desired gender. Hormone therapy is considered a partially reversible intervention[64, 65] and, according to the Dutch protocol, it should be offered when gender dysphoric adolescents are 16 years old[55, 60]. This intervention is considered sufficiently safe and has the ability to enhance the individual's mental as well as physical health[57, 59].

The final stage of gender transitioning is the contemplation of surgical interventions, which are considered irreversible procedures. Protocol differences exist across countries and centres, but surgery is never carried out on patients <18 years of age, in line with the WPATH Standards of Care [3]. Both hormonal and surgical intervention options are discussed with patients in detail, and during the decision-making process some may choose to undergo only hormonal treatment.

The use of gender reassignment in adults was pioneered in the 1920s, but no corresponding procedure for gender dysphoric children and adolescents was available until the late 1990s. Since then, puberty suppression has become increasingly accepted as an early intervention in young individuals with clear signs of gender dysphoria[64, 65].

[H3] Suppressing puberty

Suppression of puberty involves the use of GnRHa to halt the progression of puberty by blocking the activity of the GnRH receptor at the pituitary level, which results in decreased gonadotropin release. As a consequence, the reduced gonadal stimulation leads to a decrease in the expression of sex steroids, preventing the development of sexual characteristics or causing them to regress to a certain extent, if the individual has already gone through some phases of pubertal development (Figure 1). Puberty suppression is considered a fully reversible procedure[64, 65] and has been proven to be sufficiently safe[68]. Suppression of puberty in children with gender dysphoria has

the fundamental benefit for children of giving them time to reflect on their gender identity, obtain real-life experience living as the non-natal gender in dress and behaviour, and determine whether or not they desire the full transition[46]. In our opinion, as the development of a body contrary to the experienced gender has been associated with several psychosocial distress parameters, puberty suppression can be considered a preventative treatment. The procedure has consistently been linked to an improved transition into the desired gender role, including in terms of physical appearance, and a more satisfactory outcome, even in the long-term[40-42]. Nevertheless, the importance of continuing to facilitate and support further research on the effects of GnRHa cannot be overemphasized.

[H1]Conclusions

In order to better understand the implications of GnRHa for the psychological and physical wellbeing of individuals with childhood onset gender dysphoria in the long-term, further studies are needed to directly compare adolescents who underwent an early intervention protocol including puberty suppression and adolescents who did not. To date, the absence of robust data in support or against the use of GnRHa in the clinical management of childhood onset gender dysphoria has lead to inconsistencies between the approaches recommended by health care professionals across different centres. The paucity of published research on the effects of GnRHa on health-related outcome measures calls for studies which might help to advance the evidence-based debate on risks and benefits of puberty suppression. However, careful review of the available data does enable the definition of a number of safety criteria for its use (Box 4). Despite a limited number of studies, the existing literature supports puberty suppression as an early, sufficiently safe, and preventive treatment for gender dysphoria in childhood and adolescence.

Key points

Puberty suppression by gonadotropin-releasing hormone analogues is prescribed to relieve the distress associated with pubertal development in adolescents with gender dysphoria and thereby to provide space for further exploration.

Treating prepubertal individuals with gender dysphoria is still particularly controversial due to their more unstable pattern of gender variance compared to gender dysphoria adolescents and adults.

The absence of robust data in support or against the use of puberty suppression in childhood onset gender dysphoria has lead to inconsistencies between health care pathways across different centres.

The paucity of evidence of the effect of puberty suppression on health-related outcome measures calls for studies which might help to advance the evidence-based debate on risks and benefits of it.

Despite a limited number of studies, the existing literature supports puberty suppression as an early, sufficiently safe, and preventive treatment for gender dysphoria in childhood and adolescence.

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Competing interests

The authors declare no competing interests.

Biographies

Dr Rosalia Costa, General Adult Psychiatrist, developed a clinical and research interest in gender dysphoria during her residency programme in psychiatry at the University of Bari, Italy, working in a Gender Unit for adults. In 2013 she joined the Tavistock and Portman NHS Foundation Trust's Gender Identity Development Service, London, UK, where she has been expanding her knowledge of the clinical management of children and adolescents with gender dysphoria.

Dr Polly Carmichael, Consultant Clinical Psychologist, is the Clinical Director of the Tavistock and Portman NHS Foundation Trust's Gender Identity Development Service, London, UK, a highly specialist nationally designated service for young people presenting with difficulties with their gender identity.

Dr Marco Colizzi, General Adult Psychiatrist, developed a clinical and research interest in gender dysphoria during his residency programme in psychiatry at the University of Bari, Italy, working in a Gender Unit for adults. In 2013 he joined the Institute of Psychiatry, Psychology & Neuroscience at King's College London, UK, where he is working on a PhD on the neurocognitive and neurochemical effects of cannabinoids on the human brain. He has been collaborating with the Tavistock and Portman NHS Foundation Trust's Gender Identity Development Service for his research.

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Box 1 | DSM-5 diagnostic criteria for gender dysphoria in adolescents and adults (302.85/F64.1)

A. A marked incongruence between one's experience/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experience/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).

2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experience/expressed gender (or in young adolescents, the desire to prevent the development of the anticipated secondary sex characteristics).

3. A strong desire for the primary and/or secondary sex characteristics of the other gender.

4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).

5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).

6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g. a congenital adrenogenital disorder such as congenital adrenal hyperplasia or androgen insensitivity syndrome).

Coding code: Code the disorder of sex development as well as gender dysphoria.

Specify if:

Posttransition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen-namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g. penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Box 2 | DSM-5 diagnostic criteria for gender dysphoria in children (302.6/F64.2)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):

1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).

2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.

3. A strong preference for cross-gender roles in make-believe play or fantasy play.

4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.

5. A strong preference for playmates of the other gender.

6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.

7. A strong dislike of one's sexual anatomy.

8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Box 3 | Tanner stages

Pubic hair (both male and female)

Tanner 1: no pubic hair at all (typically age 10 and under)

Tanner 2: small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females) (age 10–11)

Tanner 3: hair becomes more coarse and curly, and begins to extend laterally (age 12–14)

Tanner 4: adult-like hair quality, extending across pubis but sparing medial thighs (age 13–15)

Tanner 5: hair extends to medial surface of the thighs (age 16+)

Genitals (male)

Tanner 1: prepubertal (testicular volume less than 1.5 ml; small penis of 3 cm or less)

Tanner 2: testicular volume between 1.6 and 6 ml; skin on scrotum thins, reddens and enlarges; penis length unchanged

Tanner 3: testicular volume between 6 and 12 ml; scrotum enlarges further; penis begins to lengthen to about 6 cm

Tanner 4: testicular volume between 12 and 20 ml; scrotum enlarges further and darkens; penis increases in length to 10 cm and circumference

Tanner 5: testicular volume greater than 20 ml; adult scrotum and penis of 15 cm in length

Breasts (female)

Tanner 1: no glandular tissue; areola follows the skin contours of the chest (prepubertal)

Tanner 2: breast bud forms, with small area of surrounding glandular tissue; areola begins to widen

Tanner 3: breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast

Tanner 4: increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast

Tanner 5: breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla

Box 4 | Safety criteria for puberty suppression

1. Puberty suppression cannot be provided until Tanner stage 2 or 3 is reached

    a. age ≥ 12 years, safely above the gender constancy achievement

    b. sufficient experience of one's one natal gender

2. Puberty suppression should be offered after extensive evaluation of the condition, as possible associated psychosocial risk factors and family issues could affect the decision to start the treatment

a. The condition must exhibit clear early onset; persistence and/or increase upon entering puberty and high gender-dysphoria-related distress levels are likely to predict a positive outcome of puberty suppression

b. In the presence of psychiatric comorbidities and/or not full understanding of the child's associated difficulties, the possibility of delaying puberty suppression should be considered and the psychological support should become more relevant

c. Support from parents or carers is needed and difficulties in the relationship between patients and their parents or carers should be addressed, considering specific forms of psychotherapy

3. The decision to start puberty suppression is taken only after considering patients' and their carers' concerns and expectations after being fully informed on treatment options and expected outcome

a. potential risks and benefits of proceeding or not proceeding with the treatment should be discussed with patients and their parents or carers, in light of the still limited research evidence

b. psychoeducation, counselling, and informed consent should be provided to patients and their parents or carers, in order to achieve a full understanding and realistic expectations about the treatment effects

4. An agreed decision between health-care professionals, patients, and family members should be pursued

a. the health-care providers' role is to support and facilitate patients and their parents or carers' decision

b. disagreements between patients and their parents or carers should be fully addressed, in light of the child's limited ability to make decisions and the need for parents or carers to provide informed consent on their behalf

Figure 1 | Puberty suppression

Suppression of puberty involves the use of GnRHa to halt the progression of puberty by blocking the activity of the GnRH receptor at the pituitary level, which results in decreased release of the gonadotropins LH and FSH. As a consequence, the reduced gonadal stimulation leads to a decrease in the release of sex steroids (testosterone from the testes and estrogen from the ovaries). Without exposure to the sex steroids, the body does not undergo the changes associated with them (the development of secondary sexual characteristics) which occur during the phases of pubertal development.

CNS, central nervous system; GnRHa, gonadotropin-releasing hormone analogues; LH, luteinizing hormone; FSH, follicle-stimulating hormone